DMD

DRUG METABOLISM AND DISPOSITION

# Recirculatory Pharmacokinetic Model of the Uptake, Distribution, and Bioavailability of Prochlorperazine Administered as a Thermally Generated Aerosol in a Single Breath to Dogs

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## ABSTRACT:

A thermal aerosol generation process is capable of delivering pure drug reliably to the alveoli where it is absorbed systemically. Although deep lung absorption of drugs administered as an aerosol has been shown to be rapid, detailed characterization of their absorption and distribution has not been reported. The present study describes the pharmacokinetics of prochlorperazine from the moment of administration as either a rapid intravenous infusion or a thermally generated aerosol and determines the bioavailability of the aerosol by two independent methods. Prochlorperazine disposition was determined in four anesthetized dogs after a 5-s intravenous infusion and after thermally generated aerosol administration in one breath. Venous blood samples were collected frequently from the time of drug administration to 24 h and left ventricular blood samples were drawn more often until 10 min after drug administration. Prochlorperazine disposition after intravenous and aerosol administration was characterized by fitting a recirculatory model to left ventricular and venous drug concentration data simultaneously. Prochlorperazine aerosol administration produced plasma drug concentrations similar to those after rapid intravenous administration of the same nominal dose, with peak left ventricular concentrations achieved in less than 30 s. Plasma concentration profiles of prochlorperazine administered by both routes were well described by the recirculatory model. Bioavailability of the thermally generated aerosol was consistent and averaged more than 80% of emitted dose. Pulmonary administration of a thermally generated drug aerosol in one breath may be a viable alternative to rapid intravenous administration of drugs requiring rapid and predictable production of effective plasma concentrations.

Prochlorperazine is a piperazine phenothiazine indicated for the control of severe nausea and vomiting. Prochlorperazine has also been reported to relieve the pain associated with migraine headache when administered intravenously as 10 mg of prochlorperazine edisylate in an emergency department setting (Jones et al., 1989; Coppola et al., 1995; Tanen et al., 2003). Slow absorption and low oral bioavailability due to high hepatic extraction limit the value of oral prochlorperazine for such acute therapy (Taylor and Bateman, 1987; Isah et al., 1991). A different mode of prochlorperazine administration would offer a valuable therapeutic alternative if it could produce effective plasma drug concentrations as rapidly and predictably as those provided by intravenous administration and could be used safely by the patient without the assistance or supervision of a medical professional.

A thermal aerosol generation process analogous to smoking can deliver pure drug substance reliably to the alveoli without thermal degradation products (Rabinowitz et al., 2004). Rapid vaporization of

a thin film of drug at a relatively low temperature produces a pure drug vapor that cools and condenses into 1- to 3-$\mu$m-diameter aerosol particles. Because these particles are inhaled in one breath and absorbed systemically, this process can produce peak plasma drug concentrations in less than 60 s.

Others have attempted to model systemic drug disposition after aerosolized drug input. Mather et al. (1998) reported the limitations of assuming first-order absorption in fitting aerosol data. They observed that pulmonary drug absorption might be better described with a multiphasic input, but had not collected blood samples early enough or often enough to allow them to do this. We have developed a recirculatory pharmacokinetic model that is capable of describing drug distribution from the moment of rapid intravenous administration (Krejcie et al., 1996a, 1997; Avram et al., 1997) and can be readily adapted to describe the rapid uptake of an aerosol. Nondiscrete delay elements are important components of recirculatory models, enabling description of pulmonary blood flow (cardiac output) and alveolar drug distribution volume, and should be able to describe pulmonary drug uptake as a multiphasic input (Figs. 1 and 2). Drug disposition in the early moments after rapid intravenous or aerosol administration

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**ABBREVIATIONS:** AUC, area under the concentration-time curve; MTT, mean transit time; C.O., cardiac output.
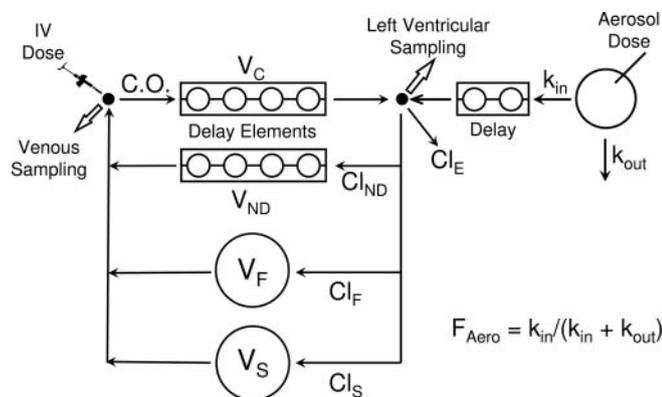
FIG. 1. The general model for the simultaneous analysis of the recirculatory pharmacokinetics of prochlorperazine (Krejcie et al., 1996a) administered as a thermally generated aerosol and as a 5-s intravenous infusion to the same animal at a different time. Aerosol drug delivery was modeled as the proportion of drug absorbed through a delay element (represented by a rectangle surrounding two cells) to describe the noninstantaneous appearance of the drug in the body. In the model, $k_{in}$ and $k_{out}$ were determined from the left ventricular first-pass pharmacokinetic data. The bioavailability of prochlorperazine when administered as an aerosol ($F_{Aero}$) was determined by $k_{in}$ and $k_{out}$, as indicated by the equation in the figure. Cardiac output (C.O.) flows through the central circulation, which is defined by the delay element ($V_C$). All delay elements are represented by rectangles surrounding two or four cells, although the number of cells needed in a delay varied between two and five. Beyond the central circulation, cardiac output distributes to tissues lumped on the basis of their volume to distribution clearance ratios (mean transit times), into the nondistributive peripheral circuit ($V_{ND}$, $CL_{ND}$), and the fast ($V_{T-F}$, $CL_{T-F}$) and slow ($V_{T-S}$, $CL_{T-S}$) tissue volume groups. The elimination clearance ($CL_E$) is assumed to occur from the left ventricular sampling site.
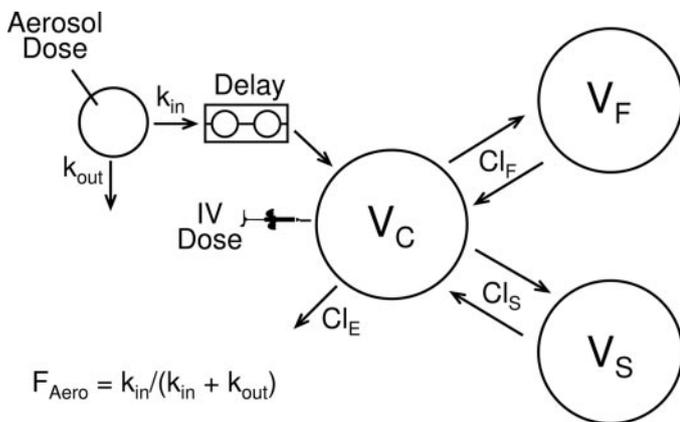


FIG. 2. The traditional three-compartment mammillary pharmacokinetic model for the simultaneous analysis of the pharmacokinetics of prochlorperazine administered as a thermally generated aerosol and as a 5-s intravenous infusion to the same animal at a different time. Aerosol drug delivery was modeled as the proportion of drug absorbed through a delay element (represented by a rectangle surrounding two cells) to describe the noninstantaneous appearance of the drug in the body. In the model, $k_{in}$ was fixed (large) and $k_{out}$ was adjusted along with the other parameters describing the pharmacokinetic data. The bioavailability of prochlorperazine when administered as an aerosol ($F_{Aero}$) was determined by $k_{in}$ and $k_{out}$, as indicated by the equation in the figure.

(front-end kinetics) described by the recirculatory model is a major determinant of the rate of onset of effect for a drug with a rapid onset of action (Krejcie and Avram, 1999).

The purpose of this study was to develop a recirculatory model to describe the pharmacokinetics of prochlorperazine from the moment of administration either as a rapid intravenous infusion or as a thermally generated aerosol to dogs. The recirculatory model was used to quantitate the bioavailability of prochlorperazine, which was also measured in the usual manner. The results of the recirculatory pharmacokinetic model were then compared with

those of a standard three-compartment pharmacokinetic model of the venous data.

## Materials and Methods

**Experimental Protocol.** Four female mongrel dogs, weighing 20.4 to 21.8 kg (20.8 ± 0.7 kg), participated in this nonrandomized, sequential study at Charles River Laboratories (Worcester, MA) after local Institutional Animal Care and Use Committee approval. All animals received two treatments separated by 48 h washout periods and were anesthetized for each treatment. Each animal received 7 mg of prochlorperazine base (6.71 ± 0.56 mg emitted dose[1]) administered during a single deep inhalation as a thermally generated aerosol created by an automated aerosol administration system connected in-line to the endotracheal tube. The aerosol was administered in the first third of the inhalation volume and followed by clear air so that the aerosol would have the greatest chance of depositing in the alveoli. The second treatment consisted of a 5-s manual intravenous (saphenous vein) infusion of 7 mg of prochlorperazine (1.4 ml of a 5 mg/ml prochlorperazine edisylate solution).

On the day of the study, after an overnight fast during which the dog was allowed water ad libitum, the animal was brought to the laboratory where it was premedicated with atropine sulfate (0.02 mg/kg i.m.) and acepromazine (0.2 mg/kg i.m.). Ten minutes later, anesthesia was induced with propofol (4–8 mg/kg i.v.), the trachea was intubated, and anesthesia was maintained with isoflurane delivered through a volume-regulated ventilator. Hydration was maintained with lactated Ringer's solution administered intravenously at a rate of 5 ml/kg/h.

Catheters for pharmacokinetic blood sampling were placed into the left ventricle via carotid arteriotomy and into a jugular vein before administering each dose. The left ventricular catheter was removed after collecting the 10-min left ventricular blood sample. The jugular venous catheter was removed between 30 and 60 min, and subsequent venous samples were drawn from the cephalic vein at a forelimb.

Left ventricular and jugular venous blood samples were collected before each treatment. Left ventricular samples were then collected every 5 s after beginning each treatment to 30 s, then every 10 s to 60 s, at 75, 90, 120, 150, and 180 s, and at 5 and 10 min. Venous blood samples were collected at 15, 30, 60, 120, and 180 s, at 5, 10, 20, 30, 60, 120, and 240 min, and at 8, 12, 16, and 24 h after commencing drug administration.

**Analytical Methods.** Plasma prochlorperazine concentrations were measured by CTBR Bio-Research Inc. (Senneville, QC, Canada), using liquid chromatography-tandem mass spectrometry after sample preparation by solid-phase extraction. In brief, 100 $\mu$l of 1.6 $\mu$g/ml $^2H_3$-prochlorperazine (internal standard) solution was mixed with 400 $\mu$l of all plasma samples, which were then alkalinized with 1 M sodium bicarbonate, and applied to conditioned Oasis HLB solid-phase extraction columns (Waters Chromatography, Milford, MA) from which they were eluted with 400 $\mu$l of acetonitrile after a water wash. Extracts were analyzed by an API 3000 LC-MS/MS system (MDS Sciex, Concord, ON, Canada) equipped with an Agilent 1100 series HPLC system (Agilent Technologies, Santa Clara, CA). Samples were subjected to gradient elution from a Synergi 4 $\mu$m Hydro-RP 80A column (50 × 3.0 mm; Phenomenex, Torrance, CA) with a mobile phase consisting of 10 mM ammonium acetate in water, pH 3 (solvent A) and 0.05% formic acid in acetonitrile (solvent B) (gradient 30% solvent B to 0.5 min, 30–90% solvent B from 0.5 to 3.0 min, and 90% solvent B to 5 min) at a flow rate of 0.5 ml/min. The turboionspray source of the tandem mass spectrometer was operated in the positive ionization mode. The mass-to-charge ratio of the precursor-to-product ion reaction monitored for prochlorperazine was 374.2 → 140.8. Drug concentrations were calculated by comparing prochlorperazine/internal standard ratios to a standard curve (2.0–400 ng/ml prochlorperazine) prepared in dog plasma. The prochlorperazine retention time was 3.39 min. The limit of quantitation of the plasma prochlorperazine assay was 2.0 ng/ml with intra-

[1] The mean ± S.D. emitted aerosol dose of 6.71 ± 0.56 mg and mass median aerodynamic particle diameter (MMAD) of 2.2 ± 0.1 $\mu$m are based on an average of three samples taken before and three taken after administration to the dogs. In brief, the emitted aerosol was collected on a filter and the quantity of prochlorperazine collected was measured by high performance liquid chromatography as described in Rabinowitz et al. (2004).

assay coefficients of variation ranging from 4.6 to 12.6% and interassay coefficients of variation ranging from 8.6 to 12.0%.

**Pharmacokinetic Models.** Plasma prochlorperazine concentration versus time relationships were modeled in two ways, both using the SAAM II software system (SAAM Institute, University of Washington, Seattle, WA) implemented on a Windows-based (Microsoft, Redmond, WA) personal computer. Left ventricular and venous plasma drug concentrations were modeled with a modification of the recirculatory compartmental pharmacokinetic model used previously to model plasma arterial and venous lidocaine concentrations (Fig. 1) (Krejcie et al., 1997), as described below. Plasma drug concentrations were also modeled with a traditional three-compartment mammillary pharmacokinetic model (Fig. 2). In both models, aerosol drug absorption was described using a tanks-in-series delay element (represented by a rectangle with two cells) to characterize the noninstantaneous first appearance of the drug in the body. In these models, the rate constants $k_{in}$ and $k_{out}$ determine only the fraction of the drug absorbed (bioavailability), as described below; the rate of absorption is characterized by the delay element and the associated mean transit time, which is also described below. The SAAM II objective function used was the extended least-squares maximum likelihood function using data weighted with the inverse of the model-based variance of the data at the observation times (Barrett et al., 1998). Systematic deviations of observed data from the calculated values were sought using the one-tailed one-sample runs test (results not shown), with $p < 0.05$, corrected for multiple applications of the runs test, as the criterion for rejection of the null hypothesis. Model misspecification was sought by visual inspection of the measured and predicted drug concentrations versus time relationships.

Model fits to the data were assessed on the basis of the coefficients of variation associated with the adjustable parameters for each model (Metzler, 1986). The fits of the models were also assessed by calculating the adjusted $r^2$ ($r^2_{Adj}$) for each model for each animal. The "adjustment" makes $r^2$ more comparable over model fits with different numbers of observations by using the degrees of freedom in its computation. It is a ratio of mean squares instead of sums of squares and is calculated as $1-$ (Mean Square Error)/(Mean Square Corrected Total).

Data collected after both the 5-s intravenous drug administration and the crossover aerosol drug administration were modeled simultaneously for each dog. Because bioavailability of the intravenously administered dose was assumed to be 100%, simultaneous estimation of pharmacokinetic parameters for both routes of administration permitted calculation of the bioavailability of the emitted prochlorperazine aerosol dose ($F_{Aero}$):

$$F_{Aero} = k_{in}/(k_{in} + k_{out}) \quad (1)$$

where the rate constants were constrained so as to have no effect on the uptake profile, which was determined by the delay element (see below). That is, in order for the combined model of the intravenously administered dose and the inhaled (i.e., aerosol) dose to have the same volumes and clearances without systematic errors in the fit of one of the two simultaneously modeled data sets, the aerosol dose had to be corrected for any drug not reaching the central compartment. The modeling program did this by adjusting $k_{out}$ and making a portion of the aerosolized dose unavailable, $k_{out}/(k_{in} + k_{out})$, so that the $AUC_{0\rightarrow\infty}$ values of the plasma drug concentration histories were consistent with the administered doses ($F_{Aero}Dose_{Aero}/AUC_{Aero\ 0\rightarrow\infty} = Dose_{i.v.}/AUC_{i.v.\ 0\rightarrow\infty}$).

A recirculatory multicompartmental model of drug disposition based on frequent early left ventricular blood sampling (Fig. 1) is able to describe drug disposition from the moment of administration (Krejcie et al., 1996a; Krejcie and Avram, 1999). Fitting the recirculatory pharmacokinetic model to the data began with fitting the first-pass data using the distributed delay elements of the SAAM II kinetic analysis software (Krejcie et al., 1996b). These delay elements are composed of $n$ compartments connected by identical rate constants $k$ such that $n/k$ is equal to the mean transit time (MTT) for the delay. Since the number of compartments, $n$, in a model is not adjustable during parameter optimization, we fit closed form equations for distributed delays in sequence to the first-pass data using TableCurve2D software (ver 5.0; Systat Software, Inc., Point Richmond, CA). First, left ventricular prochlorperazine concentration versus time data before evidence of recirculation (i.e., first-pass data) for the 5-s intravenous administration dose and the aerosol dose were weighted

uniformly and each fit by a gamma distribution function, which allows $n$ to be any positive value (i.e., permits fractional compartments):

$$C(t) = \frac{k^n \cdot t^{n-1}}{(n-1)!} \cdot e^{-kt} \quad (2)$$

Then an Erlang distribution function in which $n$ from the gamma distribution function was rounded to the nearest integer value and fixed as a constant was fit to the data. The Erlang function represents the gamma distribution with $n$ confined to integer values (i.e., permits only whole compartments).

From these first-pass left ventricular fits, we determined cardiac output, $F_{Aero}$, the model-predicted maximum left ventricular plasma prochlorperazine concentration ($C_{max}$) and its associated time ($t_{max}$), the mean transit times from sites of drug administration to the left ventricle, and the central compartment volume ($V_C$) of each model for the two routes of administration.

Cardiac output (C.O.) was estimated from the prochlorperazine dose (Dose$_{i.v.}$) and the area under the first-pass left ventricular plasma prochlorperazine concentration versus time relationship ($AUC_{i.v.\ First-pass}$) after the 5-s intravenous administration (Meier and Zierler, 1954):

$$C.O. = Dose_{i.v.}/AUC_{i.v.\ First-pass} \quad (3)$$

This cardiac output was assumed to be the same as that during administration of the aerosol dose (Dose$_{Aero}$). In the recirculatory models, the sum of intercompartmental and elimination clearances was constrained to equal this estimated cardiac output (Krejcie et al., 1996a).

Bioavailability of the aerosol dose ($F_{Aero}$) was calculated from the cardiac output and the area under the first-pass left ventricular plasma prochlorperazine concentration versus time relationship after aerosol administration (AUC$_{Aero\ First-pass}$) of the nominal aerosol dose (Dose$_{Aero}$). Since the estimated absorbed dose (Dose Est$_{Aero}$) is equal to the product of cardiac output and AUC$_{Aero\ First-pass}$,

$$C.O. \cdot AUC_{Aero\ First-pass}/Dose_{Aero} = Dose\ Est_{Aero}/Dose_{Aero} = F_{Aero} \quad (4)$$

To estimate the central compartment volumes for the 5-s intravenous dose administration data and the aerosol dose administration data ($V_{C-i.v.}$ and $V_{C-Aero}$, respectively), it was first necessary to calculate the mean transit times for the two routes of administration. MTTs were calculated from the number of cells in the central delay element ($n$ from the Erlang distribution function) and the rate constant exiting each cell ($k$ from the Erlang distribution function):
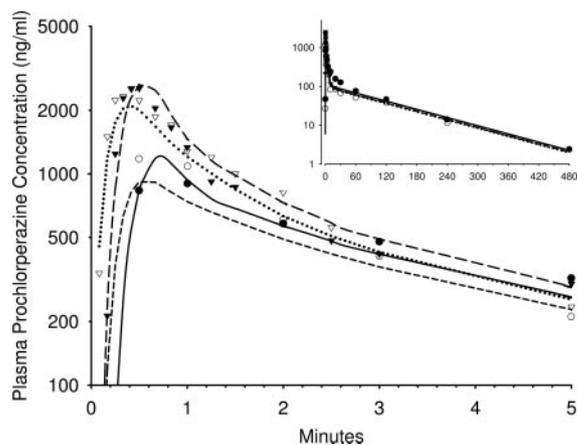
$$MTT = n/k \quad (5)$$



FIG. 3. Left ventricular and venous plasma prochlorperazine concentration histories for the first 5 min and for 480 min (inset) after administration as a thermally generated aerosol (open triangle-dotted line, left ventricular data; open circles-short dashed line, venous data) and as a 5-s intravenous infusion (closed triangle-long dashed line, left ventricular data; closed circles-solid line, venous data) for dog 3. The symbols represent the measured prochlorperazine concentrations, whereas the lines represent concentrations predicted by the recirculatory model resulting from the simultaneous analysis of the pharmacokinetics of prochlorperazine administered as a thermally generated aerosol and a 5-s intravenous infusion to the same animal at different times.

TABLE 1

*Peak plasma drug characteristics of 7 mg of prochlorperazine (nominal dose) delivered as a 5-s intravenous infusion and as a thermally generated aerosol in a single breath to dogs*

Data are listed as mean $\pm$ S.D. ($n = 4$).

| Route of Drug Administration | Predicted by Recirculatory Pharmacokinetic Model | | Observed | |
|---|---|---|---|---|
| | $t_{max}$ | $C_{max}$ | $t_{max}$ | $C_{max}$ |
| | *min* | *ng/ml* | *min* | *ng/ml* |
| Intravenous over 5 s | 0.56 $\pm$ 0.18 | 3277 $\pm$ 612 | 0.50 $\pm$ 0.14 | 3482 $\pm$ 767 |
| Aerosol in a single breath | 0.38 $\pm$ 0.05 | 3156 $\pm$ 777 | 0.33 $\pm$ 0.07 | 3262 $\pm$ 975 |

TABLE 2

*Pharmacokinetic parameters for prochlorperazine recirculatory and three-compartment models*

Data are listed as mean $\pm$ S.D. ($n = 4$).

| Parameter | Parameter Description (See Figs. 1 and 2) | Recirculatory Model | Three-Compartment Model |
|---|---|---|---|
| Volumes (liters) | | | |
| $V_C$ | Central compartment volume of the three-compartment model | N.A. | 2.09 $\pm$ 1.01 |
| $V_{C-IV}$ | Central circuit volume of the recirculatory 5-s intravenous administration model | 1.98 $\pm$ 0.43 | N.A. |
| $V_{C-Aero}$ | Central circuit volume of the recirculatory aerosol administration model | 1.64 $\pm$ 0.57 | N.A. |
| $V_{ND}$ | Nondistributive peripheral circuit volume | 0.46 $\pm$ 0.36 | N.A. |
| $V_{T-F}$ | Rapidly equilibrating (fast) tissue compartment volume | 3.18 $\pm$ 1.90 | 5.94 $\pm$ 1.48 |
| $V_{T-S}$ | Slowly equilibrating tissue compartment volume | 28.55 $\pm$ 5.94 | 27.57 $\pm$ 8.26 |
| $V_{SS}$ | Total (steady-state) volume of distribution | 34.18 $\pm$ 5.87 | 35.59 $\pm$ 9.67 |
| Clearances (l/min) | | | |
| $CL_{ND}$ | Nondistributive peripheral circuit clearance | 1.01 $\pm$ 0.73 | N.A. |
| $CL_{T-F}$ | Clearance to the rapidly equilibrating (fast) peripheral tissue compartment | 0.77 $\pm$ 0.46 | 2.68 $\pm$ 1.31 |
| $CL_{T-S}$ | Clearance to the slowly equilibrating peripheral tissue compartment | 0.79 $\pm$ 0.31 | 0.89 $\pm$ 0.19 |
| $CL_E$ | Elimination clearance | 0.40 $\pm$ 0.02 | 0.39 $\pm$ 0.07 |
| $\Sigma CL$ | Sum of all clearances, equals prochlorperazine dilution cardiac output determined from the first-pass AUC following intravenous administration | 2.97 $\pm$ 0.87 | 3.95 $\pm$ 1.45 |
| $t_{1/2\beta}$ (hr) | Elimination half-life | 1.39 $\pm$ 0.22 | 1.38 $\pm$ 0.29 |
| $r^2_{Adj}$ | Adjusted $r^2$ | 0.943 $\pm$ 0.037 | 0.837 $\pm$ 0.122 |

N.A., not applicable.

To account for the 5-s intravenous injection time, the MTTs from the intravenous route were corrected by subtracting 2.5 s from the Erlang results. The central volumes were then calculated from the respective mean transit times and cardiac output:

$$V_C = \text{C.O.} \cdot \text{MTT} \qquad (6)$$

In subsequent pharmacokinetic analyses, the description of the central circulation based on the left ventricular plasma concentration data after intravenous administration was incorporated as a fixed delay element into the recirculatory model describing both left ventricular and venous plasma drug concentrations using SAAM II (Krejcie et al., 1996b, 1997). Peripheral drug distribution can be lumped into identifiable volumes and clearances: a nondistributive peripheral pathway ($V_{ND}$ and $CL_{ND}$); rapidly equilibrating (fast) tissues ($V_{T-F}$ and $CL_{T-F}$); and slowly equilibrating tissues ($V_{T-S}$ and $CL_{T-S}$). The nondistributive peripheral pathway (delay element) represents pathways with minimal apparent tissue distribution. The parallel rapidly and slowly equilibrating tissues correspond to the fast and slow compartments of traditional three-compartment pharmacokinetic models, $V_F$ and $V_S$, respectively; therefore, the central circulation and nondistributive peripheral pathway are detailed representations of the ideal central volume of the three-compartment model, $V_C$ (Avram and Krejcie, 2003). Because of the direct correspondence between the recirculatory model and three-compartment models, $CL_E$ was modeled from the left ventricular (sampling) compartment to enable comparison of these results with those of the traditional three-compartment mammillary pharmacokinetic model.

## Results

The left ventricular plasma prochlorperazine concentrations after a single breath aerosol administration increased more rapidly than those after the 5-s intravenous infusion (Fig. 3). Left ventricular plasma

drug concentrations were *observed* to peak near 3500 and 3300 ng/ml at an average of 30 and 20 s after 5-s intravenous and single breath aerosol administration, respectively (Table 1). After peaking, the concentrations declined in parallel, with both the left ventricular and the venous plasma drug concentrations from single breath aerosol administration slightly below those from 5-s intravenous administration after approximately 3 min.

Table 2 shows the recirculatory model parameters. Although there were slight systematic errors in the fit of the recirculatory model to the very early left ventricular and venous plasma drug concentrations, simultaneous recirculatory modeling of both left ventricular and venous plasma prochlorperazine concentration versus time data collected after aerosol administration and intravenous injection resulted in a good fit of the model to the data for each dog (Fig. 3). The $r^2_{Adj}$ values for the fit of the recirculatory model to the data were all 0.89 or higher (Table 2). Eighty-two percent of the coefficients of variation associated with the seven adjustable parameter estimates for the recirculatory model of each dog (i.e., 23 of the 28 parameters for the four dogs) were less than 0.20, and all but one were less than 0.41. The maximum left ventricular plasma drug concentrations ($C_{max}$) *predicted* by the recirculatory model were approximately 3300 and 3200 ng/ml, whereas the respective predicted times to maximum concentrations ($t_{max}$) averaged 34 and 22.5 s for prochlorperazine delivered as a 5-s intravenous infusion and as a thermally generated aerosol in a single breath to dogs (Table 1).

Simultaneous modeling of data collected after both the 5-s intravenous and the single breath aerosol drug administration with a traditional three-compartment mammillary pharmacokinetic model
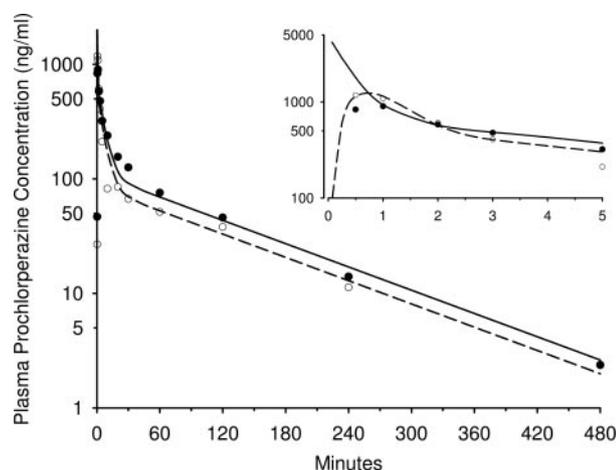
FIG. 4. Venous plasma prochlorperazine concentration histories for 480 min after administration as a thermally generated aerosol (open circles, dashed line) and as a 5-s intravenous infusion (closed circles, solid line), and for the first 5 min (inset) in dog 3 The symbols represent the measured prochlorperazine concentrations, whereas the lines represent concentrations predicted by the three-compartment model resulting from the simultaneous analysis of the pharmacokinetics of prochlorperazine administered as a thermally generated aerosol and a 5-s intravenous infusion to the same animal at different times.

(Fig. 2) also resulted in a good fit of the model to the data for each dog (Fig. 4). Ninety-four percent of the coefficients of variation associated with the nine adjustable parameter estimates for the three-compartment model of each dog (i.e., 30 of the 36 parameters for the four dogs) were less than 0.60 and all were less than 0.75. The three-compartment pharmacokinetic model parameters are summarized in Table 2. In addition to its inability to describe the very early drug concentrations observed after rapid intravenous and aerosol drug administration (Fig. 4) (which is reflected in the smaller adjusted $r^2_{Adj}$ for the three-compartment models in Table 2), the three-compartment description of drug distribution differs from that of the recirculatory model in several ways. The most important differences are its 2-fold higher estimate of $V_{T-F}$ and its 4-fold higher estimate of $CL_{T-F}$, as a result of which the sum of intercompartmental clearances, $\Sigma CL$, is 33% higher than cardiac output.

Bioavailability estimates are based on the 6.71-mg emitted dose of prochlorperazine aerosol (see footnote 1) (Table 3). The recirculation model provides estimates of bioavailability based on first-pass data (eq. 3) as well as the model (eq. 1). The bioavailability (mean ± S.D.) estimated from first-pass data, 84 ± 29% (range 44–105%), was similar to that estimated by the model, 85 ± 19% (range 57–99%) but was more variable. The mean transit time of the absorption delay element of the recirculatory model was 0.55 ± 0.05 min (range 0.50–0.59 min). Bioavailability estimated for the three-compartment model was 81 ± 9% (range 74–93%), whereas the mean transit time of the absorption delay element was 0.74 ± 0.13 min (range 0.57–0.88 min). Bioavailability estimated by noncompartmental analysis was 84 ± 16% (range 74–108%).

## Discussion

The thermally generated aerosol administration of prochlorperazine in a single breath to intubated and anesthetized dogs produced left ventricular plasma drug concentrations equivalent to those produced by a 5-s intravenous administration of the same nominal dose of the drug at least as rapidly and predictably (based on the similarities of the CVs of the data in Table 1). One apparent difference between thermal aerosol and intravenous administration is slightly more rapid appearance of drug in the left ventricle over the first 10 s after aerosol

TABLE 3

*Fraction absorbed ($F_{Aero}$) from the thermally generated aerosol administered in a single breath to dogs calculated by three methods from the two pharmacokinetic models and model independently*

Data are listed as mean ± S.D. ($n = 4$).

| Model: Analysis | $F_{Aero}$ | Absorption Delay Element Mean Transit Time |
|---|---|---|
| | | *min* |
| Recirculatory model: First-pass | 0.84 ± 0.29 | 0.52 ± 0.05 |
| Recirculatory model: Entire model | 0.85 ± 0.19 | 0.55 ± 0.04 |
| Three-compartment model: Entire model | 0.81 ± 0.09 | 0.74 ± 0.13 |
| Model independent: Venous $AUC_{0 \to \infty}$ ratios | 0.84 ± 0.16 | N.A. |

N.A., not applicable.

delivery (Table 1; Fig. 3), which is consistent with the shorter first-pass left ventricular mean transit time of the aerosol in the recirculatory model (Table 3; discussed below).

The present study is, to our knowledge, the first to describe the uptake, distribution, and bioavailability of a drug administered as a thermally generated aerosol in a single breath with a recirculatory pharmacokinetic model. The good simultaneous fit of the recirculatory model to both venous and left ventricular plasma prochlorperazine concentration versus time data after aerosol and rapid intravenous drug administration (Fig. 3) suggests that the distribution pharmacokinetics of the drug is unaffected by the route of administration. This is confirmed by the simultaneous fit of the three-compartment pharmacokinetic model to venous plasma prochlorperazine concentration versus time data after both aerosol and rapid intravenous administration without systematic deviations of the observed data from the calculated values or model misspecification (Fig. 4).

The average bioavailability of prochlorperazine administered as a thermally generated aerosol to dogs estimated by all four methods was 81 to 85% of the emitted dose. The similarity of the estimates of bioavailability determined by the first-pass AUC and the AUC of the entire disposition model indicates that virtually all systemic absorption of prochlorperazine was via immediate pulmonary alveolar uptake. The possibility of absorption via slower sites (e.g., the airway mucosa) could not be examined in the present study because the drug was administered through an endotracheal tube.

Others have studied the systemic delivery of a drug as an aerosol. Mather et al. (1998) studied fentanyl, a basic amine like prochlorperazine, administered as an aerosol by a metered dose oral inhaler. They reported that pulmonary and intravenous fentanyl administration produced similar plasma drug concentrations. Although they reported total bioavailability of the various doses of aerosolized fentanyl to be 81 ± 32%, only approximately 55% of the dose was absorbed in the first 5 min. Unlike the present study, the study by Mather et al. (1998) was not able to model pulmonary drug delivery because they started sampling too late and too infrequently after drug administration.

The frequent left ventricular and venous sampling in the current study was critical to enabling accurate modeling of pulmonary drug absorption. Nondiscrete (i.e., tanks-in-series) delay elements in the mammillary and recirculatory models enabled description of pulmonary uptake of the drug aerosol. In addition, the delay elements of the recirculatory model characterized pulmonary blood flow (cardiac output), central volume, and nondistributive blood flow. The delays in these models provide drug molecule transit-time frequency histograms that portray the fraction of drug molecules that arrive at the sampling point over time and is described statistically by a gamma

distribution function. For a tanks-in-series delay element, such as those used in the present pharmacokinetic models (Figs. 1 and 2), an Erlang frequency distribution is used because the number of cells in the delay has to be an integer value. Because this is a statistical description, the AUC for a gamma or Erlang distribution is one (i.e., the fraction of molecules arriving after an infinite amount of time is one). Therefore, to describe the concentration-time profile, the frequency distribution function is scaled (i.e., it is multiplied by the actual AUC of the drug). There is only one fastest transit time (discrete lag), but some transits can be quite delayed. This results in a distribution that is skewed to the right. For a right-skewed distribution, the mean value (mean transit time) is longer than (to the right of) the peak concentration ($C_{max}$ or the mode of the frequency distribution). As a result, the times to peak or maximum concentrations, $t_{max}$ (Table 1), are shorter than the corresponding mean transit times (Table 3).

The delay times estimated independently here for prochlorperazine by both the recirculatory and three-compartment models were less than 1 min (Table 3). The slightly longer estimated delay time of the three-compartment model may reflect the less frequently sampled venous plasma drug concentrations compared with the more frequently sampled left ventricular plasma drug concentrations from which the shorter estimates of the recirculatory model were derived.

In each dog, for the single breath aerosol compared with 5-s intravenous administration, the first-pass left ventricular mean transit time was shorter ($0.55 \pm 0.04$ min versus $0.70 \pm 0.21$ min, respectively) and the $V_c$ smaller ($1.64 \pm 0.57$ liters versus $1.98 \pm 0.43$ liters, respectively; Table 2). These differences are consistent with the circulatory anatomy. The intravenous dose transited a portion of the systemic venous drainage, the right heart, the pulmonary artery, and pulmonary arterioles in addition to transiting alveolar capillaries, pulmonary veins, and the left heart and distributing to alveolar tissue like the single breath aerosol dose. The difference between the mean transit times for the respective dosing routes can, therefore, be viewed as the time required for the intravenous dose to transit these additional pathway components, whereas the difference between the $V_C$ values represents venous, right heart, and pulmonary artery volumes.

The simultaneous fit of the left ventricular and venous plasma prochlorperazine concentration data with the recirculatory model uses the same modeling approach that we applied to intravenously administered lidocaine and antipyrine (Krejcie et al., 1997). Nonetheless, there were some aspects of this recirculatory modeling that merit comment.

Arterial drug concentrations versus time data collected before recirculation were fit to the sum of two Erlang distributions in our earlier studies in dogs (e.g., Krejcie et al., 1996a,b, 1997; Avram et al., 1997, 2000) and humans (Avram et al., 2004). The choice of the dual central circulation pathway model over a single pathway model in those studies was based on both subjective and statistical assessments (Krejcie et al., 1996b). The frequency of arterial blood sample collection in those studies, typically every 2 s for the first 30 s and every 4 s for the next 32 s, made the dual pathway model the parsimonious choice. In the present study, left ventricular blood samples drawn every 5 s for the first 30 s and then every 10 to 60 s did not support choosing a dual central circulation pathway model rather than a single pathway model on either subjective or statistical grounds. This single delay may contribute to the systematic errors in the fit of the recirculatory model to the very early left ventricular and venous plasma drug concentrations (Fig. 3).

The description of prochlorperazine pharmacokinetics by the recirculatory compartmental model (Fig. 1) is similar to those estimated by the traditional three-compartment pharmacokinetic model (Fig. 2) as

seen in Table 2. The principal difference in parameter estimates between the two models is in the volume of the rapidly (fast) equilibrating tissue compartment ($V_{T-F}$) and the intercompartmental clearance to that compartment, $CL_{T-F}$. We have demonstrated that nonrecirculatory compartmental models based on drug concentration histories obtained after rapid intravenous administration overestimate not only initial distribution volume, $V_C$, but also $V_{T-F}$ and $CL_{T-F}$ (Avram and Krejcie, 2003). We have also demonstrated that an accurate description of drug distribution with a traditional compartmental model is best based on drug concentration histories obtained after drug administration by a brief (e.g., a 2-min) infusion (Avram and Krejcie, 2003).

The present results show that inhalation of thermally generated aerosols can produce left ventricular and venous drug concentration profiles that are similar to those after rapid intravenous administration. They furthermore suggest that pulmonary administration of a thermally generated drug aerosol in a single breath may offer a viable alternative to rapid intravenous administration for drugs requiring rapid and predictable production of effective plasma drug concentrations.

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